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THE INFINITELY SMALL IN BIOLOGY[1]

By THOMAS M. RIVERS, M.D.

DIRECTOR OF THE HOSPITAL OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH

INFECTIOUS diseases and contagion were recognized many centuries before the causes of these phenomena were known or understood. Bacteria, which are considered to have been discovered by Leeuwenhoek in 1675, were known and had been studied for nearly two centuries before they were definitely associated with disease. The names of Dujardin, Davaine, Ferdinand Cohn, Koch and Pasteur stand out in the consciousness of every one as being associated with the proof that microorganisms are the cause of infectious maladies. Indeed, the labors of bacteriologists between the years 1840 and 1890 so clearly established the fact that microscopic animals and plants are the cause of infectious diseases that it became heresy to hold that such diseases might be produced in any other way.

[1] Address presenting Dr. Wendell M. Stanley to receive the 1941 Gold Medal of the American Institute of the City of New York, February 6.

In 1872, Ferdinand Cohn reported that Chaveau and Klebs had passed pus through compact filters consisting either of clay cylinders or membranes and that the material passing through the filters was not capable of producing disease. In other words, the contagious elements in the pus which were considered to be bacteria were retained by the filters. Later, Pasteur, because of his inability to see anything of causative or etiological significance in material capable of producing hydrophobia, suggested that there might be infectious agents smaller than visible bacteria. In 1892, Iwanowski, working with tobacco mosaic, passed juice from an infected plant through a filter and noticed that the filtrate was capable of producing disease in healthy plants. At the time little attention was paid to this observation, but in 1898 Beijerinck made a similar observation. He was impressed by its importance because he could see nothing in the filtrate

and could cultivate no bacteria from it. In spite of the absence of visible bodies, the filtrate was highly infectious and the disease caused by it could be passed in series through a large number of plants. He spoke of the infectious agent in the filtrates as a "living fluid contagium" in order to indicate that he thought it to be different from ordinary bacteria. In the same year Loeffler and Frosch showed that foot-and-mouth disease of cattle is caused by a filterable agent and Sanarelli demonstrated that infectious myxomatosis, a tumor-like malady of rabbits, likewise is induced in a similar manner. Shortly after this a number of diseases were found to be caused by agents so small that they could not be held back by filters capable of retaining ordinary bacteria. Thus, very quickly there was brought together late in the history of infectious diseases a group of maladies now known as "filterable virus diseases." In other words, the story of viruses and virus diseases as a group is a relatively recent one extending over a period of about 42 years.

The early observations on the filterability of tobacco mosaic virus were readily confirmed, but promptly differences in opinion arose regarding the nature of this incitant of disease. A number of bacteria and even some protozoa have been considered the causative agent, but in due course most workers arrived at the conclusion that an organism capable of cultivation on an artificial medium is not responsible and that infectious units of the active agent are too small for resolution by means of ordinary light. In 1935, Dr. Wendell M. Stanley reported the results of work in which he was able to obtain from the juice of plants infected with tobacco mosaic virus large amounts of a crystalline protein possessing all of the characteristics of the incitant of the disease. This protein has been shown to be a nucleoprotein. In addition, it has been demonstrated that a number of other plant viruses are of a similar nature and some of them have been crystallized.

While a few investigators previously had stated that a chemical agent instead of a microorganism is responsible for tobacco mosaic, Stanley was the first to bring a respectable amount of proof that infectious diseases are not of necessity caused only by microorganisms. Stanley's findings, which have been confirmed, are extremely important because they have induced a number of investigators in the field of infectious diseases to forsake old ruts and seek new roads to adventure. As much as many bacteriologists hate to admit it, Stanley's proof that tobacco mosaic virus is a chemical agent instead of a microorganism is certainly very impressive. Moreover, every one admits that the agent of tobacco mosaic is transmissible indefinitely in series from plant to plant, a fact beyond dispute, indicating abundant multiplication or reproduction of the virus. Inasmuch as reproduction is usually considered an attribute of life, great confusion and consternation have been caused. In fact, the results of Stanley's work had the effect of demolishing bombshells on the fortress which Koch and his followers so carefully built to protect the idea that all infectious maladies are caused by living microorganisms or their toxins. In addition, his findings exasperate biologists who hold that multiplication or reproduction is an attribute only of life. In the midst of the wreckage and confusion, Stanley, as well as others, finds himself unable at the present time to decide whether the crystalline tobacco mosaic virus is composed of inanimate material or living molecules. In fun it has been said that we do not know whether to speak of the unit of this infectious agent as an "organule" or a "molechism."

Dr. Wendell M. Stanley, who has wrought this upheaval in the world of infectious diseases, was born on August 16, 1904, in Ridgeville, Indiana. He received his B.S. degree from Earlham College, Richmond, Indiana, in 1926, his M.S. from the University of Illinois in 1927 and his Ph.D. from the same institution in 1929. He was a national research fellow in Munich, Germany, in 1930–31. In 1931 he received an appointment on the staff of The Rockefeller Institute, becoming a member in 1940. Dr. Stanley was awarded the American Association for the Advancement of Science prize in 1936, the Isaac Adler prize by the Medical School of Harvard in 1938, the Rosenberger Medal by the University of Chicago in 1938, the John Scott Medal, certificate and premium of the City of Philadelphia in 1938, for studies on the biochemistry of viruses. He received the honorary degree of doctor of science in 1938 from Earlham College, Harvard University and Yale University.

Dr. Stanley is a chemist and has achieved fame early in life. He announced the discovery for which he is receiving the medal to-night five years ago, when he was thirty-two years of age. Not only has he developed rapidly, but he carried out the early part of his work on the crystallization of the virus in the face of opposition. Five or six years ago very few biologists or chemists thought it worth while to spend much time in attempting to crystallize infectious agents. This story reminds one somewhat of the record of another pioneer in the field of infectious diseases, Louis Pasteur, who as a chemist made outstanding contributions in the field of infectious diseases, often in the face of opposition. In still another respect, Dr. Stanley is like Pasteur; he is a master of exposition and knows well how to defend his work.

I have already mentioned several virus diseases. This group of maladies is large and includes many more than those mentioned, for example, infantile paralysis, St. Louis type of encephalitis, Japanese type B encephalitis, equine encephalomyelitis, small-

pox, vaccinia, yellow fever, human influenza, swine influenza, measles, chickenpox, shingles, lymphogranuloma inguinale, pseudo-rabies, cattle plague, leucosis of fowls, Rous's sarcoma of chickens, peach yellows, curly top of beets, aster yellows and bacteriophagy. This partial list leaves no doubt in the mind of any one that the virus group of maladies is an extremely important factor in the physical and economic well-being of man.

In addition to the immediate importance of virus diseases, there is a more remote one of a philosophical trend which has to do with the nature and origin of their causative agents. A consideration of this phase of the problem eventually leads to a discussion of the nature and origin of life. As every one knows, this discussion was started many years ago. In 1872, it was already well under way in relation to bacteria which at that time were considered the smallest of living things or as Pouchet expressed it "the infinitely small in biology." Indeed, Cohn in an article of that year made the following statement: "Through these facts we surely have a right to hope that in the development of bacteria the key will be found to the origin of life in the world in general."

Scientists of seventy years ago were hoping to find in a study of bacteria an answer to questions about the origin and nature of life. After a time it was realized that these small entities are not simple but quite complex and that it would be unlikely to find in a study of them all the secrets of the origin and nature of life. When a group of infectious agents, the viruses, was found, members of which are smaller than ordinary bacteria, when it was realized that some of them are much smaller than ordinary bacteria even approaching in size that of certain protein molecules, and when a few of these infectious agents were shown to be crystalline proteins, the old discussions regarding the origin and nature of life and what constitutes "the infinitely small in biology" were resurrected and clothed in new garments. Dr. Stanley has played a leading rôle in these discussions and has said and done many things to arouse the curiosity of numerous investigators in many and diverse fields of science.

In these times when the world is greatly disturbed by wars and rumors of wars, it is nice to take a recess from anxiety about what is going to happen to us and our cherished institutions and pay tribute to a man who seeks to make life on this earth more profitable and pleasant. In this connection there comes to mind a statement made by Louis Pasteur in 1888:

> Two contrary laws seem to be wrestling with each other nowadays; the one, a law of blood and of death, ever imagining new means of destruction and forcing nations to be constantly ready for the battlefield—the other a law of peace, work, and health, ever evolving new means of delivering man from the scourges which beset him.
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> The one seeks violent conquests, the other the relief of humanity. The latter places one human life above any victory; while the former would sacrifice hundreds and thousands of lives. . . .

Mr. President, I have the privilege of presenting to you for the high honor of the Gold Medal of the American Institute of the City of New York, a true pioneer in science, one investigating "the infinitely small in biology," a man respected and honored by his colleagues, my friend, Dr. Wendell M. Stanley.

SOME CHEMICAL, MEDICAL AND PHILOSOPHICAL ASPECTS OF VIRUSES[1]

By Dr. W. M. STANLEY

MEMBER OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, PRINCETON, N. J.

I DEEPLY appreciate the high honor which is conferred by this presentation of the Gold Medal of The American Institute of the City of New York for crystallizing the virus of tobacco mosaic. However, I should perhaps say that I greatly doubt that the crystallization of tobacco mosaic virus which I accomplished in 1935 was the first time that this material had been crystallized. It has been known for years that crystalline inclusions occur within the cells of certain mosaic-diseased plants. Within the past few years, evidence was obtained that this crystalline material consists almost exclusively of tobacco mosaic virus; hence, credit for first crystallizing this virus must go to nature. It might be expected that I should be able to claim to have been the first person to bring about the crystallization of this material. However, I believe that even this is denied me. In 1904 Iwanowski prepared stained sections of mosaic-diseased leaves and noted that the addition of an acid fixative caused the formation of a "striate material." I think, in view of present-day knowledge, that the striate material was crystalline tobacco mosaic virus which was induced to crystallize by the addition of the acid fixative. Therefore, to Iwanowski, who is already credited with the discovery of viruses in 1892, must also go the credit for the first crystallization of a virus. Now, in order to forestall the beginnings of wonderment in the minds of some of you as to why we should be gathered here

[1] Address accepting the 1941 Gold Medal of the American Institute of the City of New York.

to-night, let me hurry on to say that, judging from their writings, neither Iwanowski nor any of the persons who subsequently described the striate material envisioned the possibility that it might be in fact tobacco mosaic virus. It is obvious, therefore, that this medal is not being awarded for the simple feat of crystallizing this material, but rather because the isolation of the crystalline protein in 1935 was accompanied by the realization that it might be tobacco mosaic virus, because of the subsequent work which has demonstrated beyond a reasonable doubt that it is crystalline tobacco mosaic virus, and especially because of the impact which a full realization of the diverse implications of this fact is having and will have upon the thoughts and actions of scientists.

Before entering upon a discussion of these implications, I should like to digress for just a few moments and tell you something of the events which preceded the isolation and crystallization of tobacco mosaic virus. The Board of Directors of The Rockefeller Institute decided to establish a Laboratory of Plant Pathology at Princeton in 1931 in conjunction with the then existing Department of Animal Pathology, so that comparative studies of diseases of plants, animals and man could be carried out within a single organization. The director, Dr. Flexner, and the newly selected leader of this group, Dr. Kunkel, invited me to go to Princeton to do chemical work on viruses. Although I hardly knew the correct definition of a virus, I was in a receptive mood for this invitation, for my interest in the application of chemistry to medical problems had been awakened during my years as a graduate student in organic chemistry with Roger Adams at the University of Illinois and nurtured by a year's study on sterols with Wieland in Munich and by a year with Dr. Osterhout at the Institute in New York. It seemed to me that the biological activity represented by a given virus must belong to some tangible entity and, whether it be an organism, molecule, "molechism" or "organule," it should be possible by chemical methods to purify, concentrate and eventually isolate this entity and learn something of its general nature. I knew that Dr. Kunkel was firmly convinced, like most people, as Dr. Rivers has already pointed out, that viruses were merely still smaller living organisms, but I also knew that Dr. Kunkel, unlike many others, was nevertheless firmly convinced of the advisability of conducting chemical investigations on viruses. Furthermore, at that time the work of Allard and others, especially that of Dr. Vinson, who was associated with Dr. Kunkel at the Boyce Thompson Institute, had demonstrated that one virus, namely, tobacco mosaic virus, could be manipulated successfully by ordinary chemical methods. This pioneer work of Vinson and others was very important because it indicated that, regardless of its nature, tobacco mosaic virus was susceptible to chemical attack.

Another event which had just occurred and which was to have a great influence on the chemical work was the demonstration by Dr. Holmes that tobacco mosaic virus would cause local lesions or spots on the leaves of certain plants and that the number of these spots could be used as an index of the virus concentration in the inoculum. In earlier work it had been very difficult, following separation of a given virus preparation into two or more fractions, to determine which fraction contained most of the virus. The local lesion method did not receive immediately the attention which it merited. It was, however, used extensively throughout the course of the chemical work at Princeton and the importance of the fact that by means of this technique differences of 10 to 20 per cent. in virus concentration could be determined readily can not be overestimated. Another happy circumstance was the location of the Laboratory of Plant Pathology only about 100 yards from Dr. Northrop's laboratory, where it had just been demonstrated that certain enzymatic activities were the specific properties of certain protein molecules. The latter fact and a close and cordial association with Dr. Northrop and his coworkers had a profound influence on the course of the chemical work on the plant viruses. Also of great importance was the fact that by virtue of the location of the chemistry laboratory in a Department of Animal and Plant Pathology, it was possible to consult animal or plant pathologists at a moment's notice and through them to gain access to a tremendous store of knowledge of viruses. As a matter of fact, in retrospect, it is difficult to see how the combination of the factors which I have just described could have resulted otherwise than in the isolation and crystallization of tobacco mosaic virus. In many different ways the time was most opportune. It is obvious, therefore, that the event which is being celebrated to-night came about as the result of the interplay of many factors, each of which was of such importance in its own right that its omission might have delayed for years the result that has been achieved. Thus, the Gold Medal Award honors the many individuals associated with these factors and stands as a symbol of the importance of the culmination of these factors in the isolation and crystallization of tobacco mosaic virus and of the influence which this has had and may be expected to have in many different fields of scientific endeavor.

Dr. Rivers has told you that viruses as disease-producing agents have been recognized for only about 42 years but that during most of this time the general consensus of opinion has been that these agents are very small organisms. However, the material which was isolated and crystallized in 1935 and which carried

all the virus activity of the starting material proved to be a nucleoprotein which was larger than any protein heretofore known. The immediate task which presented itself was to prove that the virus activity either was or was not a specific property of this unusually large nucleoprotein. This was, or at least appeared to be, a rather simple chemical problem. It was found that this same material having constant chemical and biological properties could be obtained not only from mosaic-diseased Turkish tobacco plants but also from many other species of mosaic-diseased plants. The amount isolable was found to vary greatly and to depend upon the nature of the host. The material could be taken into solution and recrystallized, subjected to different types of chemical manipulation, passed through fine collodion membranes, and mixed with other biologically active as well as inactive proteins and reisolated without causing a loss of the virus activity. Many attempts based on diverse techniques were made to separate the virus activity from the nucleoprotein, but none was successful. Of special significance is the fact that by one type of chemical treatment it was possible to cause structural changes in the large nucleoprotein and loss of virus activity, but by reversing the structural changes the virus activity was regained. This result and the other experiments which I have described briefly are all compatible with the idea that the virus activity is a specific property of the nucleoprotein.

However, if the nucleoprotein is tobacco mosaic virus, then it should occur solely in mosaic-diseased plants and should not occur in plants diseased only with other viruses. It was soon found that plants diseased with certain other viruses contained different amounts of high molecular weight nucleoproteins, but that in each case the amount and the properties of the nucleoprotein which was isolated were different and characteristic of the virus. A more severe test was provided by the examination of the same type of host plant diseased with different strains of tobacco mosaic virus. This resulted in the isolation of quite similar nucleoproteins which, however, occurred in different amounts and possessed slightly different properties that have in each case proved to be characteristic of the given strain. These results demonstrated that in every case the nucleoprotein isolated was always characteristic of the infecting agent regardless of the host, the virus or the strain of the virus. On the basis of the experiments which I have described and many more which can not be discussed because of lack of time, it was concluded that the large nucleoprotein was in fact tobacco mosaic virus. This conclusion did not receive universal acceptance, and I well remember the many arguments which ensued. Fortunately, the trend of the opposing argument was usually the same and was to the effect that viruses were living organisms; hence the crystalline nucleoprotein could not possibly be the virus, for obviously it was not an organism. It was always assumed that the virus activity accompanying the nucleoprotein was due to contaminating organisms. When asked to describe the properties of these organisms, it was usually stated that they had the same properties as those of the nucleoprotein, which of course must be the case if the organisms were to remain undetected by the searching chemical, physical and serological examination to which the preparations had been subjected. I suppose that such a possibility must always be granted, but from a practical standpoint it is obvious that it is absolutely unnecessary to postulate the existence of two entities when one is sufficient to satisfy the data.

Because no opposing argument more serious than the one I just mentioned has been advanced, but more especially because during the ensuing years there has issued from laboratories all over the world a great mass of experimental data which indicated that the virus activity is a specific property of the nucleoprotein, there has come to be an almost universal acceptance of the idea that the nucleoprotein is tobacco mosaic virus. This idea is accepted so completely in my laboratory that we work with and think of tobacco mosaic virus much as we would with simple organic molecules. I have already indicated that we have inactivated and reactivated the virus by bringing about and then reversing certain structural changes. Recently Dr. Anson and Dr. Miller were able to cause different kinds of structural changes without inactivating the virus. It is significant that these changes in structure not only did not inactivate the virus but were not perpetuated in subsequent generations. Still other relatively minor changes in structure have been found to cause inactivation. It is obvious that by focusing the chemical attack on different points of the architecture of the molecule, it should be possible to determine whether virus activity results from some force emanating from essentially the whole structure or from an unusual field of force localized at some definite position or positions. This is thrilling work, for, because of the peculiar nature of virus activity, a change in structure may result in a loss of activity or result in the retention of activity either with or without the perpetuation of the structural change in subsequent generations. The second possibility is important because it would correspond to the mutation of a virus induced by known structural changes with the formation of a new active structure which presumably would cause a new disease. Each of the three possibilities has deep-seated medical implications which I shall discuss in a few moments.

At this time I should like to tell you about some rather interesting special properties of tobacco mosaic virus. Solutions of this virus exhibit what is known

as double refraction of flow. When examined by means of polarized light, the flowing stream is found to be doubly refracting, whereas when quiescent the same material is not doubly refracting. This property may prove of importance in apparently unrelated fields for, because of it, solutions of tobacco mosaic virus could be used to study the flow currents in apparatus such as pumps and hydraulic rams or the nature of the flow when boats or projectiles move through the liquid. If the solution of virus is sufficiently concentrated, it may gradually separate out into two layers, the lower of which is spontaneously doubly refracting and the upper of which shows double refraction only when caused to flow. Because of this behavior, it has been inferred that the particles of the virus are not spherical but markedly anisometrical in shape. By means of indirect methods, Dr. Lauffer estimated that the virus molecules were about 400 mμ in length and about 12 mμ in width and had a molecular weight of about 40 millions. From x-ray data, Bernal and Fankuchen inferred that the virus molecules had a diameter of 15 mμ and a length of some value greater than 150 mμ. They also suggested that the needle-like virus crystals described in 1935 consisted of these molecules arranged laterally in two-dimensional hexagonal close packing and that this form of the virus should be referred to as para-crystalline but that the individual molecules had such a regular internal structure that each molecule was in effect a single crystal.

It has been stated that the asymmetry and molecular weight values obtained for tobacco mosaic virus by certain indirect methods are wholly ambiguous, but it has always been my opinion that these values were reasonably valid. However, it is obvious that, because of the relatively small size of the virus particles, a means for their direct mensuration has been lacking. Fortunately, a new approach to this general problem was provided recently by the development of electron microscopes having resolving powers extending down to about 5 mμ. Since the limit of resolution for visual light is about 250 mμ and most viruses are known to range in size from about 250 mμ down to about 10 mμ, this new apparatus offered for the first time the possibility of securing pictures of the individual particles of such viruses and thus of establishing their sizes and shapes with some precision. The Radio Corporation of America, through Dr. Zworykin, has generously made an electron microscope available to us and by means of this instrument Dr. Anderson has secured many micrographs not only of tobacco mosaic virus but of other viruses. In the case of tobacco mosaic virus, the micrographs showed a preponderance of particles having a length of about 280 mμ and a width of about 18 mμ and served to prove beyond a reasonable doubt that this virus is rod-like in shape. Earlier micrographs obtained by Kausche and Ruska had also shown a rod-like shape for this virus. The size and distinctive shape of tobacco mosaic virus make it an admirable subject for study under the electron microscope. The reaction between this virus and a gold sol having spherical particles about 40 mμ in diameter has been studied by Kausche and Ruska and recently Dr. Anderson and I were able to follow the interaction of molecules of tobacco mosaic virus with certain smaller molecules. The electron microscope has also made it possible to confirm earlier indirect evidence that two or more molecules of virus may combine end-to-end to form long aggregates. The nature of the forces which are responsible for this peculiar type of aggregation is unknown. Langmuir and also Levine recently showed that there are good theoretical grounds for the existence of interparticle forces effective over large distances, and Bernal has made use of these in a theory of the duplication of chromosomes. It is obvious that the electron microscope has opened up new fields of research and has provided a new method of attack on older problems.

The medical aspects of viruses are perhaps the most important and intriguing not only from a scientific standpoint but also from a personal standpoint, since most of us have at some time suffered from one or more attacks of a virus. In the absence of living cells, these agents appear as harmless and as lifeless as pebbles on a beach, yet even after years of inactivity some viruses may spring into action and cause disease and death when introduced by chance or by design into certain living cells. It is at this point that we are being forced to the greatest revision of our ideas, for the virus structures, some of which have the chemical and physical properties usually ascribed to molecules, appear to be able to enter into the metabolic chain of events within cells and so alter normal metabolic activity that replicas of the virus structure are produced. All viruses so far purified have been found to contain or to consist of nucleoprotein, and this fact may be of special significance, for the bearers of heredity which we all carry within all the cells of our bodies and which may be regarded as virus-like because of their reproductive ability have also been found to be nucleoproteins. Some workers consider it possible that viruses may be derived from genes or nuclear material. Other workers entertain the idea that the alteration of some normal intracellular constituent either by the fortuitous contact with a normal material having a structure similar to that of the sex hormones or through the action of other carcinogenic agents may result in the freeing of a virus-like entity which then dominates intracellular activity. I should perhaps mention at this point that there may be a

direct relationship between viruses and cancer, for it is conceivable that such a sequence of events might result in the inauguration of a cancerous growth. This idea can not be dismissed as being preposterous, for in 1911 Rous demonstrated that a chicken tumor was caused by a virus, and during the past few years he has shown that a close relationship exists between the Shope papilloma virus and the cancers which usually develop from the virus-induced papillomas in domestic rabbits.

It is possible that there exists within our cells masked or latent forms of viruses which may at some time be stirred into action by mutation or by some other provocative influence. Several cases of the harboring of viruses by presumably normal cells have already been discovered. For example, practically all of the potato plants grown in the United States are known to carry a virus. The plants might be regarded as normal, for the presence of this infectious agent, known as the latent mosaic of potato virus, can not be demonstrated readily so long as one works only with potato plants. Its presence can be demonstrated easily, however, by applying extracts of such plants to certain other plants, such as Turkish tobacco, which respond to the virus with obvious disease symptoms.

The roads traversed by viruses appear to be many and devious and not always apparent. Shope has recently shown that swine influenza virus may be harbored within lung worm larvae carried in turn within earthworms for many months, and that the ingestion of these earthworms by swine may result at some later date, following a provocative stimulus, in an attack of swine influenza. Although the virus can not be demonstrated directly when in the lung worm larvae within the earthworm, the results show it to be present at the start of the sequence of events and it is demonstrable at the end. The situation may be likened to that of a train going through a tunnel—you may see the train as it enters and as it leaves the tunnel, but it is not apparent while in the tunnel. This brilliant work in which a virus has been traced from a diseased host through a long and circuitous path involving two intermediate hosts back to a normal host and other work on intermediate virus hosts such as insects make one pause and wonder whether similar situations may not obtain in the cases of other virus diseases. It is already known among other things that the actual amount of virus present in a host may vary as much as 100-fold at different stages of the disease. Another point of considerable importance is the fact that some diseases result from the combined action of two infectious agents. Thus in 1926 Vanderpool showed that tomato streak was due to tobacco mosaic and potato mosaic viruses and Shope discovered that swine influenza results from the combined action of a virus and a bacterium.

Let us consider briefly some of the measures which have been taken to control the activities of viruses. Plant virus diseases represent a special case because of the nature of the plant circulatory system and the fact that plants do not appear to develop antibodies. Consequently, control measures consist largely of special methods for preventing infection and the use of resistant varieties of plants, although, as Kunkel has shown, heat treatment may be used to cure certain virus-diseased plants. There are, as you may know, three general methods which are employed in the protection of man and animals against virus diseases. In the first method, active virus is used in conjunction with immune serum. The second method, which involves the use of active virus of a strain which will cause an innocuous disease, is employed extensively and successfully against smallpox, yellow fever and certain other viruses. The strains of virus used for immunization may be secured by passing the virus through other hosts. For example, in the protection against smallpox a strain of this virus obtained by passage through calves may be used and for yellow fever a strain originally obtained by passing this virus through mouse brains is used. The change in environment during the production of virus in the second host apparently results in the formation or selection of a strain of virus which is much less virulent in the first host. We know from our work with tobacco mosaic virus that its strains consist of closely related nucleoproteins which nevertheless have slightly different properties. Recently Dr. Knight secured information concerning the nature of the chemical differences between strains of this virus. It seems likely, therefore, that passage of a virus through another host may yield a virus strain having a different chemical structure. Although at present we know little about the nature of the change or why it occurs, the work with the plant viruses indicates that eventually these problems will be elucidated. Furthermore, the production of new and useful strains of viruses by means of structural changes brought about *in vitro* by definite chemical reactions offers even greater possibilities in connection with this general method of protection.

The third general method involves the use of inactivated virus and has been used in the past with claims for success for many viruses such as rinderpest, hog cholera, dog distemper, influenza and others. The method is now being widely used in the case of equine encephalomyelitis virus. The success of this method appears to depend upon securing by chemical or physical treatment structural changes of sufficient magnitude to cause loss of virus activity but insufficient to cause much change in the antigenic properties.

In other words, the virus must be inactivated but the resulting structure must on injection be able to induce the formation of antibodies which will neutralize the active virus. This result was achieved in work with certain of the plant viruses and anti-plant-virus rabbit sera some years ago, but it was obvious from the results that each virus would have to be studied individually in order to arrive at the best method for inactivation. The problems involved are chiefly chemical in nature and they are receiving considerable attention at present. Some of you may be wondering why, with all of the information which now appears to be available, we are not protecting our general population against such virus diseases as influenza and poliomyelitis. It so happens that, although we know much about certain viruses, we know relatively little about other viruses. This is due to such factors as availability, stability, ease of titration and existence of a good experimental host, which cause one virus to be an especially favorable experimental subject and another virus to be a very poor experimental subject. For example, work with poliomyelitis virus has been especially difficult because it has been necessary to use a certain kind of monkey as the experimental host and only a very small portion of the animal contains a good concentration of virus. Therefore, the amount of diseased tissue available as starting material for experimentation is definitely limited and the titration of the virus is extremely difficult and very expensive. Factors such as these represent the bottlenecks in virus research, and as they are eliminated a burst of progress usually results. Thus, Theiler's discovery of the mouse as an experimental host for yellow fever virus and TenBroeck's discovery of the existence of a tremendously high concentration of equine encephalomyelitis virus in diseased chick embryos not only made possible new and diverse studies but led directly to methods of protection against the ravages of these two viruses. Therefore, the emphasis of the research work must in some cases be placed on ways and means for securing larger amounts of virus, in others on studies of titration methods, and in still others in a search for a good experimental host. However, it should be recognized that advances made in connection with any one virus aid greatly in the work with other viruses and that, although the fight should be pushed forward vigorously on all fronts, complete advantage should be taken of those viruses which, like tobacco mosaic virus, have already proved to be unusually favorable experimental material.

In closing I should like to discuss briefly some of the philosophical aspects of viruses. Dr. Rivers has already indicated that a consideration of the nature and origin of viruses eventually leads to a discussion of the nature and origin of life. It is possible that viruses have always been produced only by the action of viruses or of virus-like entities within cells, or that they have not always existed but arose from bacteria by a process of retrograde evolution under parasitism with loss of function and associated substance. These are examples of biogenesis, and opposed to this theory to-day as in Pasteur's day is heterogenesis or spontaneous generation, the outstanding advocate of which is Oparin, who has described in detail a possible mode of evolution of matter. Since one of the outstanding properties of viruses to-day is their dependence upon living cells for reproduction, it has been reasoned that they are the supreme representatives of obligate parasitism and hence followed cells in the process of evolution. However, other persons argue that it is but a step from synthesis *in vivo* to synthesis *in vitro* and prefer to use the viruses as proof that a molecule may duplicate itself *in vitro*. It must be admitted that the theory of heterogenesis is most challenging and would serve to explain the origin of viruses.

However, I think that there is another approach to the general problem which merits consideration. In order to have spontaneous generation, there must be a difference between living things and inanimate things and, despite the general acceptance that a difference does exist and the building on the one side of two schools of thought, vitalism and mechanism, a few feeble although penetrating voices have cried out on the other side. Over 2,000 years ago Aristotle is supposed to have said that nature makes so gradual a transition from the animate to the inanimate that the boundary line between the two is doubtful and perhaps non-existent. Spinoza expressed the concept that all matter possesses different degrees of life depending upon the organization. I believe that the virus data now available enable us to visualize this general idea with a new understanding. It is difficult, if not impossible, to place a sharp line separating living from non-living things when one considers a series of structures of gradually increasing complexity such as would be represented by hydrogen, water, benzene, ergosterol, egg albumin, insulin, pepsin, tobacco mosaic virus, papilloma virus, vaccine virus, pleuropneumonia organism, bacteria, a mammal like a dog and intervening entities. The problem is similar to that encountered when an attempt is made to determine the exact point at which one color blends into another in a color spectrum or when one attempts to establish just where acid becomes alkaline. It is possible, of course, to set up arbitrarily a point of division as has been done for acid and alkali, but this can not detract from the fact that the difference is not of a fundamental nature but merely one of degree. It has been said that living things differ from non-living things in that for the former the total is always equal to more than the sum of the parts. Yet the same is

true for even simple molecules, for, knowing only the two gases oxygen and hydrogen, who could have predicted the properties of the water molecules formed by a certain combination of these gases? It is obvious that as new structures are formed new properties characteristic of these structures are evolved. I believe that the work on viruses has provided us with new reasons for considering that life as we know it owes its existence to a specific state of matter and that the principle of the vital phenomenon does not come into existence suddenly but is inherent in all matter.

SCIENTIFIC EVENTS

EXPEDITIONS SENT OUT BY THE U. S. NATIONAL MUSEUM

TWELVE scientific expeditions were conducted by members of the staff of the U. S. National Museum during the past fiscal year. They were for a variety of purposes such as collecting animals of many kinds, fossils and geological specimens and archeological materials, many of which will serve as reference types for American scientists. These expeditions are described in the report of Dr. Alexander Wetmore, assistant secretary of the Smithsonian Institution, who is in charge of the museum.

One was an anthropological survey in Russia and Siberia by Dr. Aleš Hrdlička, curator of physical anthropology, to study remains of peoples who may have been closely related to the ancestors of the American Indians. The red men are generally believed to have been neolithic Asiatic peoples who entered North America by way of Alaska.

The eastward extension of Pueblo Indian influences into Kansas was studied by Dr. Waldo R. Wedel, of the museum staff. The builders of the great "apartment houses" of the Southwest are popularly supposed to have been confined to that part of the continent. Actually small buildings on the Pueblo model are found extending into the Great Plains area although the exact relationships between their builders and the southwesterners still remain to be found.

Dr. W. F. Foshag, curator of physical and chemical geology, collected specimens of rare minerals in Mexican mines. Dr. G. A. Cooper, with Dr. Josiah Bridge, of the U. S. Geological Survey, journeyed from Nevada to north-central Indiana in search of invertebrate fossils of the Devonian and Ordovician periods in the history of the earth. They collected many types of fossils new to the collections, including some new to science.

Dr. C. W. Gilmore, curator of vertebrate paleontology, assisted in a survey of the Big Bend region of Texas, which has been proposed for a national park. The area, he found, gives considerable promise of yielding dinosaur remains.

Dr. Leonard P. Schultz, curator of fishes, brought back a collection of about 14,000 fishes, together with mollusks, echinoderms, worms, other marine invertebrates, reptiles, birds, mammals and plants from the Phoenix and Samoan Islands. He served as naturalist on a U. S. naval expedition.

As in past years, Captain Robert A. Bartlett, who has long served as a collaborator of the museum, brought valuable specimens from Greenland waters. Among these this year was a collection of Arctic plants.

There were 2,505,171 visitors to the various buildings during the year. This is an increase of more than a quarter of a million over the year before.

THE NEW SCHOOL OF PUBLIC HEALTH OF THE UNIVERSITY OF MICHIGAN

ACCORDING to the *Michigan University Record*, the reorganization of the work in hygiene, public health and preventive medicine has been for some time under discussion. As early as August, 1939, on recommendation of the Division of Health Sciences, the regents authorized, when it should become possible, the establishment of an independent unit of the university to carry on this type of activity. It may now be announced that the W. K. Kellogg Foundation, of Battle Creek, and the Rockefeller Foundation, of New York, have each agreed to provide $500,000 for the establishment of the new school, not more than one half of the total sum of $1,000,000 to be available for site, building and equipment, and the remainder to be used over a ten-year period for its initial expenses of operation. The regents in December accepted the proffer of these sums, subject to the conditions attached, which involve both the method of applying the funds, as outlined above, and the formulation of a plan of organization satisfactory to the two foundations and the university. While progress has been made upon the scheme of organization, it has not yet reached the stage at which a detailed statement can be made public.

The long-continued interest of the Rockefeller Foundation in public health is well known. The trustees of the W. K. Kellogg Foundation are led to participate in the enterprise because of their conviction that public health education is important and a strong school of public health is essential to the success of the Michigan Community Health Project. The university is expected to use its present resources for graduate training in public health and to make certain further provisions for this work in the future.

AWARDS OF THE AMORY FUND BY THE AMERICAN ACADEMY OF ARTS AND SCIENCES

THE American Academy of Arts and Sciences announces the award of nearly $16,000 to be divided equally among four investigators for their contributions to the treatment and cure of diseases of the genito-urinary system.

The Amory Fund was established in 1912 by the will of the late Francis Amory. The income of the fund is devoted to the award of a septennial prize to be given to any individual or individuals who, in the judgment of the American Academy of Arts and Sciences, shall have made notable contributions for the treatment and cure of disease and derangements of the human genito-urinary organs. The 1941 prizes are the first to be awarded from the Amory Fund and cover contributions made since 1933.

Three of the prizes of nearly $4,000 each are to Americans and the fourth is to a scientific man in Europe in a country unhappily dominated by Nazi invaders. His name will not now be made public and his prize will be held here in trust.

The names of the three American investigators, together with an outline of their work furnishing the basis for the awards, follow:

Dr. Joseph F. McCarthy, professor and director of the department of urology, New York Polyclinic Medical School and Hospital. For thirty years Dr. McCarthy has worked intensively on the problem of developing techincal instrumental procedures for the examination, diagnosis and treatment by way of the urethra, without external incision, of certain diseases of the bladder, prostate and related organs. Working with instrumental technicians he originated a new type of electric endoscope which vastly increased the field of vision in the examination of any cavity or deep recess of the human body. He further perfected this instrument to include an electrotome or cutting device which permits the cutting away by the high-frequency current of obstructing and redundant portions of the prostate gland under actual visual inspection, and the control of resulting hemorrhage.

Dr. Carl Richard Moore, professor of zoology at the University of Chicago. The development of his investigations has led him from the study of the fertilization of the ovum—through the physiology of the spermatozoon—to the study of the physiology of the male reproductive tract of the mammal, more especially as it is influenced by the hormonal secretions of the male sex gland. It was his investigations which first demonstrated the importance of the secretion of the adult testis to the behavior of the other components of the male reproductive apparatus. His findings as to the effects of the testicular secretion on the spermatozoon, on the seminal vesicles, and on the prostate and its function have had a profound effect on subsequent investigations.

Dr. Hugh H. Young, professor of urology at the Johns Hopkins Medical School. For the relief of obstruction to the outlet of the urinary bladder caused by cancer of the prostate gland, the operation of total prostatectomy by the perineal approach as devised and perfected by the intensive labors of Dr. Hugh H. Young is of the greatest value. It has been possible by this operation not only to remove the malignancy with success, but also at the same time to preserve the normal function of the bladder.

PRIZES AWARDED BY MEMORIAL HOSPITAL, NEW YORK CITY

DR. E. L. KENNAWAY and Dr. J. W. Cook, of the Royal Cancer Hospital, London, England, have been chosen by Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, to receive its annual Katherine Berkan Judd prizes of $1,000 for outstanding contributions to knowledge of the cause and cure of cancer for 1939 and 1940. The awards are for discoveries of wide and vital importance made by the isolation from coal tar of certain chemicals which produce cancer in animals. The 1939 award was postponed to assure careful consideration of the progress and significance of various research projects in the cancer field here and abroad. Previous awards went to French and German cancer research workers.

The award was established under the will of Katherine Berkan Judd, of New York, wife of Lewis B. Judd. Mrs. Judd, who died in 1934, made Memorial Hospital the trustee of a trust fund of $30,000. From the income, an annual prize of $1,000 is given to encourage study and research in cancer, and the prize is awarded to the person contributing most to advancement in this field during the year.

Both current prizes are for a research project on which Dr. Kennaway (director of the Royal Cancer Hospital) and Dr. Cook are working together, *i.e.*, the action of specific chemical substances, particularly coal tar derivatives, in the causation of cancer. They have been seeking the origin, along chemical lines, of what is known in England as "chimney-sweep's cancer," a term originally coined by Dr. Percival Pott in 1820 when he found that some ingredient of soot (coal tar) caused an irritation from which cancer developed. In course of his investigations Dr. Kennaway established the fact that coal tar is more active at high temperatures, as it is found in chimneys. He discovered that it was the fluorescent ingredient in coal tar which was damaging. In 1929 he isolated dibenzanthracene in crystalline form and found that it was active in all animals.

Dr. Cook discovered the molecular structure, demonstrating the chemical formula of the cancer-producing agent, which was his main contribution to the work carried on by Dr. Kennaway.

The citation to Dr. Kennaway was as follows:

Dr. E. L. Kennaway, of the Royal Cancer Hospital, London, for outstanding contributions in the field of

cancer research, over a period of many years. During this period, as a broadly trained pathologist, he was an inspiring director of a notable institution of service and research, contributed to the knowledge of the public health relations of the cancer problem, and, by keen vision and persistent industry, demonstrated the carcinogenic action of specific chemical substances, thereby contributing a discovery of great fundamental importance and epoch-making significance in the history of our knowledge of cancer.

The citation to Dr. Cook reads:

Dr. J. W. Cook, of the Royal Cancer Hospital, London, for outstanding contributions in the field of cancer research. As a broadly trained chemist, by brilliant reasoning and refined technical methods, he penetrated one of Nature's most hidden secrets, revealing the exact molecular structure of carcinogenic chemical substances, thereby providing a new mode of attack on the problem of cancer genesis.

Previous recipients of this award have been Professor Claude Regaud, of the Curie Institute in Paris, for pioneer contributions in the field of radiophysiology and therapy, and Professor Robert Meyer, of Berlin, for his work in gynecological pathology at the University of Berlin.

AWARD OF THE WILLARD GIBBS MEDAL TO DR. DOISY

THE Willard Gibbs Medal for 1941 has been awarded by the Chicago Section of the American Chemical Society to Dr. Edward A. Doisy, for the past eighteen years professor of biochemistry at the School of Medicine of the Saint Louis University.

The award, made annually by the Chicago Section to a scientist "whose work in either pure or applied chemistry has received worldwide recognition," was determined by a national jury of scientific men of which Dr. William F. Henderson was chairman of the section. The medal will be presented to Dr. Doisy at a dinner meeting in the Stevens Hotel on May 23.

Dr. Doisy was assistant in biochemistry at the Harvard Medical School from 1915 to 1917, and the following two years served in the U. S. Army. From 1919 to 1923 he was on the staff of the Washington University School of Medicine as instructor in biochemistry, associate and associate professor. He joined the faculty of the St. Louis University School of Medicine in 1923.

According to the official citation, in 1929 Dr. Doisy isolated theelin, female sex hormone, and in 1936, dihydrotheelin, another sex hormone. An investigation of vitamin K directed by him in 1939 led to the isolation from natural sources such as dried alfalfa leaf meal and putrefied sardine meal of two pure substances possessing vitamin K activity. The structures of both were determined and one was produced synthetically. This work resulted in the recognition of the antihemorrhagic potency of the chemical compounds known as 1,-4-naphthoquinones.

Earlier studies included the preparation of insulin, the analysis of nervous tissue, creatine and creatinine metabolism, purine metabolism, determination of sodium, potassium, chloride and phosphate in tissues, and carbon dioxide transportation of blood.

RECENT DEATHS

DR. CHARLES VALUE CHAPIN, superintendent of health in Providence from 1884 to 1932, from 1886 to 1894 professor of physiology at Brown University, known for his work on sanitation and infection, died on January 31. He was eighty-five years old.

DR. GEORGE E. VINCENT, who was president of the University of Minnesota from 1911 to 1917, and of the Rockefeller Foundation from 1917 until his retirement in 1929, died on February 1. He was seventy-six years old.

WILLIAM CASPAR GRAUSTEIN, professor of mathematics and assistant dean at Harvard University, was killed on January 22 in an automobile accident.

DR. ANTON L. FROLIK, associate professor of agronomy at the University of Nebraska, died on January 27, at the age of thirty-three years, in the Army hospital at Fort Leavenworth, Kansas, where he was serving as a major for a year's period.

DR. LEVI WALTER MENGEL, for forty years associated with the Reading, Pa., public school system, founder and director of the Reading Museum and Art Gallery, who was ornithologist for the late Rear Admiral Robert E. Peary in 1891 on an expedition to the northernmost point of Greenland, died on February 3 at the age of seventy-two years.

MRS. MARY SWARTZ ROSE, since 1921 professor of nutrition at Teachers College, Columbia University, with which she had been connected since 1906, died on February 1 at the age of sixty-six years.

THE death is announced of Dr. Michel Weinberg, of the Pasteur Institute, Paris, known for his work in parasitology and anaerobic bacteria.

A CORRESPONDENT writes that Dr. Carl Thore Mörner, professor of medical and physiological chemistry at Uppsala University, Sweden, died on September 7 at the age of seventy-six years.

SCIENTIFIC NOTES AND NEWS

THE Walter Reed Medal of the American Society of Tropical Medicine was conferred at the Louisville meeting on Dr. Herbert C. Clark, since 1929 director of the Gorgas Memorial Laboratory of Tropical and Preventive Medicine, Panama Canal Zone, in recognition of his work on the eradication of malaria and other tropical diseases.

THE John Deere Gold Medal of the American Society of Agricultural Engineers for "distinguished achievement in the application of science and art to the soil," has been awarded to Robert William Trullinger, assistant chief of the Office of Experiment Stations of the U. S. Department of Agriculture. The Cyrus Hall McCormick Medal of the society has been awarded to H. C. Merritt, vice-president of the Allis-Chalmers Manufacturing Company, Milwaukee, for "exceptional and meritorious engineering achievement in agriculture."

DR. ALFRED BLALOCK, professor of surgery at the School of Medicine of Vanderbilt University, was presented with the research medal of the Southern Medical Association at the annual meeting in Louisville, Ky. The award was made in recognition of his "research on the circulation of the blood in cases of shock."

DR. ALEXANDER MCADIE, emeritus professor of meteorology at Harvard University, who was director of the Blue Hill Observatory from 1913 to 1931, is one of eleven on whom has been conferred honorary life membership in the Associate Alumni of the College of the City of New York.

THE award of the Annie J. Cannon prize to Mrs. Julie M. Vintner Hansen, of the Royal Observatory of Copenhagen, was made by the American Astronomical Society and not, as reported in SCIENCE, by the Rittenhouse Astronomical Society of Philadelphia.

AT the annual meeting of the American Mathematical Society at the University of Louisiana, the following officers were elected: *President,* Dr. Marston Morse, Institute for Advanced Study, Princeton, N. J.; *Vice-president,* Dr. T. Y. Thomas, University of California at Los Angeles, and *Secretary,* Dr. J. R. Kline, University of Pennsylvania.

OFFICERS of the Ecological Society of America have been elected as follows: *President,* Dr. Alfred E. Emerson, professor of zoology at the University of Chicago; *Vice-president,* Dr. B. C. Tharp, professor of botany at the University of Texas, and *Treasurer,* Dr. Royal E. Shanks, of the University of Tennessee.

PROFESSOR THOMAS J. TALBERT, chairman of the department of horticulture and forestry of the Missouri College of Agriculture, was elected president of the American Pomological Society at the fifty-sixth annual convention of the society, held on January 16 at Hamilton, Ontario.

PROFESSOR ERNEST FRANKLIN BARKER, of the University of Michigan, has been appointed chairman of the department of physics. He takes the place on February 17 of Professor Harrison M. Randall, who has retired from active service.

DR. CONRAD M. ARENSBERG, of the Massachusetts Institute of Technology, has been named head of the newly established department of anthropology and sociology at Brooklyn College.

WILLIAM LANE AUSTIN, having reached the age of seventy years, retired as director of the Census on January 25. He is succeeded by Dr. Vergil D. Reid as acting director, who has hitherto been assistant director.

DR. HARRISON E. HOWE, editor of *Industrial and Engineering Chemistry* and of the *News Edition* of the American Chemical Society, Washington, D. C., was recently appointed chemical priority executive by E. R. Stettinius, director of the Division of Priorities of the Office of Production Management.

CAPTAIN JEAN DELACOUR, ornithologist, has been appointed consultant for the future development of the New York Zoological Park. Captain Delacour, who is secretary of the International Committee of Ornithologists and president of the International Committee for Bird Preservation, lost what was said to be one of the finest private zoological and ornithological collections of the world when the Germans invaded France.

THE Committee on Scientific Research of the American Medical Association announces the following grants-in-aid: William H. Welker, University of Illinois College of Medicine, Chicago, study of water soluble proteins; W. R. Tweedy, Loyola University School of Medicine, Chicago, effect of magnesium deficient diet on serum phosphatase activity in the albino rat; Barnett Sure, Agricultural Experiment Station, Fayetteville, Ark., study of new factor in vitamin B complex essential for reproduction and lactation; Doran J. Stephens, University of Rochester, effect of undernutrition on thyroid and ovary of the guinea pig; Norris J. Heckel, Rush Medical College of the University of Chicago, effect of sex hormones on seminal fluid; Hans Popper, Cook County Graduate School of Medicine, Chicago, study of vitamin A and lipoids in tissues by fluorescence microscopy; Harry G. Day, Indiana University, Bloomington, physiological significance of zinc.

DR. ALEXIS CARREL, who retired in July, 1938, as a member of the Rockefeller Institute for Medical Research, sailed on February 1 for Europe to study the effects of malnutrition and cold on the undernourished populations of Europe. He plans to visit Spain first after landing at Lisbon, then he will go wherever his studies best can be furthered.

DR. PAUL F. KERR, professor of mineralogy at Columbia University, left on January 29 on a six months' lecturing tour of several South American countries. His trip, most of which will be made by plane, is under the auspices of the Carnegie Endowment for International Peace.

AN Associated Press dispatch reports that Dr. Elmer L. Sevringhaus, president of the Association for the Study of Internal Secretions, has received the first of the "government travel grants," which provide funds for the exchange of cultural, professional and artistic leaders between the United States and the other American republics. He will leave the United States by plane for Argentina and Uruguay late this month to acquaint colleagues there with the latest advances in endocrinology in this country.

PROFESSOR N. PAUL HUDSON, professor of bacteriology and chairman of the department of bacteriology of the College of Medicine of the Ohio State University, was given leave of absence and left in the autumn for France for work under the auspices of the Rockefeller Foundation. On his arrival there he found that conditions had so changed that he was assigned to work in London. He is now supervising the distribution of the influenza vaccine, which has been developed by one of his former students, Dr. Edwin H. Lennette.

WILLY HARTMAN, of Lima, Peru, sailed for home on January 18 after about three years of study at Cornell University and at the Bureau of Plant Industry, U. S. Department of Agriculture, in the field of genetics and plant breeding.

GEORGE DE HEVESY, of the Institute of Theoretical Physics of the University of Copenhagen, has been appointed Durham lecturer at the Harvard Medical School for the present academic year. He will deliver a series of lectures open to the public, beginning on April 28, on the "Application of Radioactive Isotopes to Biological Problems."

DR. FOREST RAY MOULTON, permanent secretary of the American Association for the Advancement of Science, gave an address at the hundred and seventy-fifth anniversary convocation of Rutgers University. His subject was "Mathematics as Related to Astronomy." In the afternoon following the convocation he conducted a symposium to which were invited professional men from Swarthmore, Princeton, the University of Pennsylvania and the Hayden Planetarium.

PROFESSOR EDWIN G. CONKLIN, of Princeton University, will deliver a course of three public lectures on the Sharp Foundation at the Rice Institute, Houston, Texas, on March 5, 6 and 7. His general subject is "What Is Man?" and the subjects of the several lectures are "The Human Species," "The Development of the Individual," "The Real and the Ideal."

DR. HOWARD B. LEWIS, professor of biological chemistry at the Medical School of the University of Michigan, will deliver the fifth Harvey Society Lecture of the current series at the New York Academy of Medicine on February 20. Dr. Lewis will speak on "The Significance of the Sulfur-Containing Amino Acids in Metabolism."

DR. W. F. G. SWANN, director of the Bartol Research Foundation of the Franklin Institute at Swarthmore, Pa., will give on February 17 the annual Sigma Xi lecture at the Polytechnic Institute of Brooklyn. He will speak on "Cosmic Rays."

DR. B. H. WILLIER, professor of zoology and head of the department of biology of the Johns Hopkins University, gave on January 31 an illustrated lecture at the Catholic University of America under the auspices of the newly organized Sigma Xi club. His subject was "Feather Color Pattern Produced by Grafting Melanophores in the Chick Embryo."

AT Kansas State College on January 31 Dr. Lancelot Hogben, regius professor of natural history at the University of Aberdeen, gave two lectures entitled, respectively, "The Nature of Man" and "Methods and Problems of Human Genetics."

DR. R. RUGGLES GATES, professor of botany in the University of London and head of the department of botany in Kings College, who left England in July of last year for a lecture tour at American educational institutions, gave a series of three lectures at the State College of Washington on January 27 and 28. The first, on "Human Evolution," was delivered at a joint meeting of the chapters of Sigma Xi of the University of Idaho and of the State College; the second, on "Plant Breeding and Recent Genetics," before the staffs in botany, genetics and plant and animal breeding, and the third, "The Amazon," at a meeting of the staff of the College of Agriculture and the Agricultural Experiment Station.

THE fourth series of the John Wyckoff Lectures at the New York University College of Medicine was delivered by Dr. John R. Paul, professor of preventive medicine at the Yale University School of Medicine, on February 4 and 5. The subject was "The Clinical Epidemiology of Poliomyelitis." These lectures were established by the Phi Delta Epsilon Fraternity in 1937 in memory of the late Dean John Wyckoff.

THE twenty-fifth annual meeting of the Pacific Divi-

sion of the American Association for the Advancement of Science is to be held at Pasadena, Calif., from June 16 to 21. There will be a survey of current research in four selected fields. Arrangements for this session are now complete. The program is as follows: "New Results in Stellar Spectroscopy" by Dr. W. S. Adams, Mount Wilson Observatory; "Recent Advances in the Study of Poliomyelitis" by Professor E. W. Schultz, Stanford University; "A Survey of Engineering Research on the Metropolitan Aqueduct" by Julian Hinds, Los Angeles, Calif.; "Recent Studies on High Blood Pressure" by Dr. Myron Prinzmetal, University of Southern California, Los Angeles.

THE annual joint meeting of the Institute of Radio Engineers and the American Section of the International Scientific Radio Union will be held on May 2 in the building of the National Academy of Sciences, Washington, D. C. The meeting is open to the public. The program will, as usual, be devoted to the more fundamental and scientific aspects of radio. A copy of the titles and abstracts of the papers to be presented can be obtained during April from Dr. J. H. Dellinger, National Bureau of Standards, Washington, D. C.

A MEETING in commemoration of the Life and Work of Alexander Dallas Bache, celebrating the one hundredth anniversary of the establishment of his magnetic observatory on the grounds of Girard College with a symposium on geomagnetism, will be held on February 14 and 15 in the Halls of the American Philosophical Society and Girard College, in cooperation with the American Philosophical Society, the U. S. Coast and Geodetic Survey, the Department of Terrestrial Magnetism, the Carnegie Institution of Washington and Girard College.

THE second annual conference of the Entomologists of the State of Maine and of the three Maritime Provinces of Canada was held at the University of New Brunswick, Fredericton, on January 22, 23 and 24. It was conducted along the same lines as the first conference held at Orono in 1940, a discussion of the insect problems of the region at the present time and what can be done to meet these problems in the immediate future. Foresters, plant pathologists, horticulturists, potato inspectors and marketing officers were asked to sit in at the conference so that the various angles of viewpoint might be brought forward.

THE Connecticut Valley Student Scientific Conference will hold its eleventh annual meeting at Mount Holyoke College on Saturday, April 12. Ten colleges of the Connecticut Valley region will participate in the conference, presenting papers and demonstrations in various fields, including chemistry, physics, mathematics, zoology, botany, geology, astronomy, physiology and psychology.

ON the recommendation of the National Advisory Cancer Council, the National Cancer Institute has made grants-in-aid to the University of Cincinnati in support of researches on the relation of gastric cancer to chronic gastritis, and on improvements in the methods of diagnosis and treatment of cancer; also to the Chicago Tumor Institute in support of research on radiotherapy of radio-resistant forms of cancer of the mouth, pharynx and larynx.

APPLICATION blanks for the first Sigma Delta Epsilon fellowship may be secured from Dr. Nina E. Gray, Illinois State Normal University, Normal, Ill. They should be sent in by March 15. Women with the equivalent of a Ph.D. degree, conducting research in the mathematical, physical or biological sciences, who need financial assistance and give evidence of high ability and promise are eligible. The appointee must devote her entire time to an approved research project.

THROUGH the bequest of the late William Campbell, for many years Howe professor of metallurgy at Columbia University, two fellowships have been established. They are awarded primarily for graduate study and research in the field of metallurgy. The stipend of each Campbell fellowship is fixed at the time of award by recommendation of the Campbell Fellowship Committee and will normally be an amount sufficient to meet the necessary living expenses of the incumbent of the fellowship. Applications accompanied by certified transcripts of academic records, statements of proposed research projects and proposed fields of graduate studies should be filed with the secretary of the university before March 1. Application blanks and announcements will be forwarded by the secretary of the university on request. For other information write to Professor Eric R. Jette, the School of Mines, Columbia University. In addition to the fellowships, it is expected that one or two assistantships in the department of metallurgy will be available for the academic year 1941–42. In each of these positions research and teaching duties are assigned, but there is ample opportunity for graduate study. Inquiries and applications for these assistantships should be sent to Professor Jette.

THE *Journal* of the American Medical Association states that the American Association for the Study of Goiter again offers the Van Meter Prize Award of $300 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The essays may cover either clinical or research investigations and should not exceed 3,000 words in length. Further information may be obtained from Dr. W. Blair Mosser, 133 Biddle Street, Kane, Pa. The award will be made at the annual meeting in Boston, which will be held on May 26, 27 and 28.

DISCUSSION

THE SYNTHESIS OF PLASTEIN

CONTROVERSY still exists as to whether plastein[1] is protein. Chen[2] by chemical procedure has investigated the nature of plastein to the extent of determining whether the enzyme used in its formation constitutes part of the final product, because if so the reaction could scarcely be classed as enzymatic. This Chen did because he states he felt the immunological work of Flosdorf, Mudd and Flosdorf[3] would lead one to suspect the enzyme to be a part of the plastein. The results of the latter workers showed that the antigenicity previously ascribed to plastein was in reality due to the enzyme used in "synthesis."

The purpose of the present communication is to point out that these immunological findings do not imply chemical combination on the part of the enzyme, as suggested by Chen. Small amounts of enzyme adsorbed or otherwise physically carried down with the precipitating plastein readily can account for the observed immunological specificity. It is not necessarily surprising that Chen was unable to detect, by the chemical procedures he used, amounts of material that are detectable by the sensitive immunological procedure of the precipitin reaction.

Concerning the controversy as to whether plastein is synthetic protein, Alcock[4] states that ". . . if there is a synthesis, it can best be described as a polymerization, and the product has little relationship with the protein from which it ultimately derived." He is disposed to regard the reaction as resulting from a "condensation function" of the enzyme. Collier[5] more recently has made further chemical investigation of the reaction and concludes that it is a true enzymatic synthesis of a protein. He does not maintain, however, that the substance is a typical protein or that the phenomenon explains protein synthesis *in vivo*. In explanation of Folley's results,[6] Collier states that because the ultracentrifugal measurements of Folley were made at a pH of 9.2, which is far on the alkaline side of the isoelectric point, the sedimentation rate may have been much too low. Collier would feel, accordingly, that Folley's findings of weights on the order of a few hundred with a maximum of 1,000 are invalid.

Collier[7] subsequently arranged for ultracentrifugal analysis in London, using isoelectric plastein dissolved in urea solution. The results showed "sedimentable material" to have been synthesized, but the material is completely inhomogeneous and is not a definite entity. Collier[8] also attempted a determination of the possible antigenicity using anaphylaxis in guinea pigs and found evidence for slight antigenicity. He did not, however, completely follow through a determination of the specificity. Although two animals given proteose plus enzyme as the test injection failed to react, two out of four animals tested with plastein also failed to react. Furthermore, 0.002 per cent. concentration of enzyme included in the test dose was far less proportionately than that which corresponds to the 4 per cent. optimal recommendation of Borsook and Wastenays for synthesis of plastein,[9] and, in any event is of a lower order of magnitude than that which could adhere to precipitating plastein.

Formerly, the known antigenicity of plastein was a cardinal point offered in favor of its being protein. The work of Flosdorf, Mudd and Flosdorf would appear to invalidate such evidence, as pointed out originally by those authors, by showing that the specificity of the antigenic material could be accounted for as of the enzyme. It might well be, of course, that plastein could be a non-antigenic protein; the immunological procedure used would not distinguish between such material and substances of molecular weight of the order reported by Folley, or "peptone polymeres" as suggested by Alcock. Experiments concerning the antigenic nature of plastein without very careful regard for the specificity of that antigenicity should not be used as evidence in the controversy; in the instance where specificity was carefully determined, the results showed that the antigenicity does not constitute evidence in favor of the possible protein nature of plastein.

EARL W. FLOSDORF
UNIVERSITY OF PENNSYLVANIA

THE USE OF PLASTIC AS A SUBSTITUTE FOR COVER GLASSES

IN SCIENCE, July 5, 1940, Vol. 92, pp. 17–18, we published a note concerning the use of plastic cover slips to take the place of glass cover slips, which can not be obtained at the present time, or can be obtained only at a very great expense.

While there were certain disadvantages connected with the substitution of this plastic material for glass, on the whole, it gave good service and the large majority of the sections stained with haematoxylin and eosin and mounted in Canada balsam were satisfactory during the first month or two. However, further experience has shown that after about four to five months many sections may become more or less decolorized. This method can therefore be used only if the sections are studied within the first two months and do not need to be preserved permanently. We are

[1] Wastenays and Borsook, *Physiol. Rev.*, 10: 110, 1930.
[2] Tung-Tou Chen, *Chin. Jour. Physiol.*, 15: 159, 1940.
[3] Flosdorf, Mudd and Flosdorf, *Jour. Immunol.*, 32: 441, 1937.
[4] R. S. Alcock, *Physiol. Rev.*, 16: 1–18, 1936.
[5] H. B. Collier, *Can. Jour. Research*, 18B: 272, 1940.
[6] S. J. Folley, *Biochem. Jour.*, 26: 99, 1932.
[7] H. B. Collier, *Can. Jour. Research*, 18B: 305, 1940.
[8] H. B. Collier, *Can. Jour. Research*, 18B: 305, 1940.
[9] H. Borsook and H. Wastenays, *Jour. Biol. Chem.*, 63: 566, 1925.

at present testing other substances which might take the place of Canada balsam and do not have the disadvantage of the latter.

V. SUNTZEFF
IRENE SMITH

WASHINGTON UNIVERSITY
SCHOOL OF MEDICINE

ADENOSINETRIPHOSPHATASE

OUR experiments corroborate the results of *W. A. Engelhardt* and *M. N. Ljubimowa*[1] according to which Adenosinetriphosphatase is bound to myosine. The enzyme is activated by Ca; Ca can be substituted by other bivalent metals.

A. SZENT-GYÖRGYI
I. BANGA

INST. OF MED. CHEMISTRY,
UNIVERSITY OF SZEGED
December 15, 1940

ANOTHER AVIVOROUS ANGLER OR GOOSEFISH

WHILE collecting (November 3, 1940) with a group of graduate students at Jamestown Beach near the mouth of Narragansett Bay, we found an angler fish (*Lophius piscatorius*) about three feet in length stranded high up on the beach, dead but in perfectly fresh condition. The previous day had been stormy, with a strong southeast wind, and since this beach is at the head of a small narrowed inlet opening toward the southeast, it had doubtless been subjected to a heavy surf on the preceding day.

This remarkable fish—the striking characteristics of which are a very broad flattened head; a rapidly narrowed, almost triangular, scaleless body with pectoral fins borne upon stout fleshy peduncles and pelvic fins superficially resembling the legs of a short-legged amphibian rather than fins of a fish; and last but not least, an enormous mouth furnished with pointed teeth hinged to bend inward (but not outward) and with a lure at the end of one of the barbels on the front of the head—is obviously an inhabitant of the bottom. However, it makes excursions to the surface, as some of its food items attest, specimens having been previously found to contain wooden lobster pot floats and other objects, including, besides fish, gulls, ducks, etc., and even to attempt, at least, to engulf geese and loons.

The present specimen contained a solid lump which upon examination proved to be a herring gull, normal in appearance except for somewhat moistened feathers. There was no evidence of air contained in the stomach or any suggestion, other than a heavy surf, of the cause of this angler becoming stranded.

While several records of the angler feeding upon birds are known,[1] few of these are American records, and it seems of interest to record this finding.

A. M. BANTA

BROWN UNIVERSITY

POOR DELIVERY OF SCIENTIFIC PAPERS

I MOST heartily concur in all that Frances H. Allen says, in SCIENCE for January 3, about the poor delivery of many papers at scientific meetings.

At the recent Philadelphia meetings I left one symposium after failing to hear the first three speakers; and an entire evening was spoiled because a very prominent scientist, who gave one of the public lectures, could not be followed by those seated back of the middle of a moderately large auditorium.

The local arrangements, at least for the American Society of Zoologists, left nothing to be desired, but I felt that a considerable part of my time had been wasted for the reason mentioned above.

ALBERT M. REESE

WEST VIRGINIA UNIVERSITY

SOCIETIES AND MEETINGS

THE AMERICAN ASSOCIATION OF SCIENTIFIC WORKERS[1]

THE symposium on "The Scientist and American Democracy" was the first effort on the part of the American Associaion of Scientific Workers to present before a large nation-wide gathering of scientists an evaluation of some phases of the interrelations between science and our democratic society. The two, well-attended sessions were presided over by Professors R. W. Gerard and A. H. Compton, and a number of outstanding American scientists gave papers dealing with four main themes.

In the introductory papers of the sessions Professors A. J. Carlson and Kirtley F. Mather discussed the scientist's concept of and his citizenly duties toward our democracy. The body of the first session was an evaluation of the scientist's relation to the material base of our technological civilization. Professor A. C. Lane summarized the implications of the scientific utilization of raw materials, Dr. C. E. Kellogg, using examples from agricultural problems, discussed the rôle which the scientist plays in determining policy in a democratic state, and Professor Walter Rautenstrauch presented a fundamental and searching analysis of our industrial and productive organization.

The body of the second session dealt with two

[1] *Nature*, 144: 668, 1939.

[1] Report on the symposium "The Scientist and American Democracy," held on December 27 and 28, 1940.

[1] Gudger, 1929, *Natural History*, Vol. 29, p. 155.

themes, the relation of the scientist to some public problems of domestic importance, and the preservation of science during the world crisis of the present war. In the first group were discussed three of the most pressing questions of the moment, Thomas F. McSweeney reporting on "Housing," Professor John P. Peters on "The Public Health," and Mr. Donald E. Montgomery on "Consumer Protection." It is significant that very great interest was evidenced by the audience and by the press in these closely reasoned papers. This attention indicated not only the urgency of the problems under discussion but also that scientists have a double interest in them, firstly as members of the democratic community and, secondly, as a group which looks forward to the solution of these problems on the basis of rational, scientific principles.

The last two papers, devoted to the question of the preservation of science, consisted of a report by President Leonard Carmichael of the methods and aims of The National Roster of Scientific and Specialized Personnel and of an examination by Dr. K. A. C. Elliott of the effects of the war on the science and scientists of the belligerent countries. Dr. Elliott's paper described activities by the A. A. S. W. on behalf of the preservation of data of European scientists and presented specific recommendations to American scientists for actions on their part to help preserve both the science and the scientists of the belligerent countries. These proposals have received wide national attention, in particular the suggestion for the safeguarding in America of European scientific data, and the suggestion that the council of the American Association for the Advancement of Science appoint a standing committee to study and initiate measures to preserve science in the belligerent countries and to aid the scientists of these countries as well as the refugee scientists who have been uprooted from their work and scattered over the world.

At the close of the meeting, a resolution was proposed by Professor Gerard and carried by the audience urging the council to take such steps. The National Committee of the American Association of Scientific Workers concurred in this resolution and transmitted it to the council.

At the first session, the president of the Association, Professor A. J. Carlson, described the scientist's concept of a democratic society as ". . . that social, economic, and political order which favors or permits the maximum of freedom and opportunity for the efforts and achievements of the individual, consistent with the common welfare, and gives the individual full or equal share in establishing, balancing, and sustaining that freedom and opportunity." Some phases of our social organism were then checked against this "blueprint," disclosing considerable divergence between the existing and the desired conditions but at the same time showing recent trends which have led to improvements. "The principle and practice of war as a national policy" was condemned by Professor Carlson as "an almost insurmountable obstacle in the path of the democratic way of life." He also emphasized that the attempt on the part of this country and of other countries to ". . . dictate, directly or under cover, the form of government for other nations . . . is worse than undemocratic, it is futile, in the long run." Since "democracy in its international relations . . . means honest and fair cooperation" Dr. Carlson challenged both the excuse of "self-defense" given by Hitler for his attacks upon his neighbors and the profession by Great Britain that it is fighting for democracy, ". . . remembering that British big business has also fought for pure democracy in far-off India and Africa for quite a spell."

At the second session, which dealt with important current problems facing society, Professor Kirtley F. Mather outlined the responsibilities of the scientist as a citizen in a democracy. Scientists "share with all other citizens in a democracy the responsibilities of rendering useful service to the community of which they are a part and of participating in the legal process of 'government by the people.' There are, however, certain responsibilities of citizenship that rest more heavily upon the scientist than upon other members of society or may even be his unique obligation. It is his mental habits that distinguish the scientist-citizen from the non-scientist-citizen. . . ." But ". . . the scientific organization of society in a democracy can be achieved only when the majority of its citizens have the scientific attitude toward social problems and act in accordance with that attitude of mind." Accordingly, "the totalitarian dictator . . . will use every weapon in his arsenal to prevent the spread of scientific habits of mind throughout the rank and file of his obedient serfs. The truly democratic leader, however, will do all he can to stimulate among his fellow citizens the desire to know all the facts and the ability to think intelligently. . . ." The scientist therefore has one task as a teacher and popularizer of science and of the scientific methods of thought. "Equally important is the responsibility that rests upon the scientist in a democracy to continue . . . unfalteringly his search for new and better ways of increasing the efficiency and comfort of mankind. Here he is beginning to find himself under a new obligation arising from the new conditions involved in twentieth century civilization.

"The great service rendered by science to society during the past four hundred and fifty years resulted largely from success in thinking on the level of invention. For the most part the relationships between the

objects and institutions thus invented were determined by the unguided operation of the principle of cause and effect or were regulated by conflict, competition, and the selection they brought in their train. Gradually however, and with increasing intensity in the last few years, man has become aware of the necessity for intelligent, purposeful regulation of these relationships. The interdependence of men in a world neighborhood makes necessary a new pattern of thought. The Age of Invention is even now giving way to the Age of Planning. . . . It is the responsibility of the scientist to make the machinery of planning consistent with the structure of the democratic society. A democratic form of coordinated control must be developed in the transition from the political state to the social service state. . . ."

HARRY GRUNDFEST,
Chairman, Program Committee
ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK

REPORTS

INDUSTRIAL RESEARCH IN THE UNITED STATES IN 1940[1]

THE total expenditure for basic production research in the United States in 1940 was probably $220,000,000. A nation-wide study was started by the Air Hygiene Foundation in attempting to reduce the estimated $900,000,000 a year lost to the industries by workers absent because of illness. The speed-up of production increases the hazards which result in many types of accidents and maladies. In a non-explosive coal-mining process a tube placed in a hole drilled in a vein expands when oil under high pressure is pumped into it. The Bureau of Mines reported on the hydrogenation of low-rank coals from the West. A satisfactory substitute for mica is needed and "Alsifilm" is being tried in lieu of mica splittings. A procedure of exploring for metal-bearing ores is based on the observation that plants growing over an ore body contain more of the metal in their tissues than plants from other places. American clays have displaced imported clays for many uses. "Duraglass" is a stronger bottle glass produced by automatic control; figured wire glass is made with chromium-plated wire. Valuable increases were reported in the light transmission of optical systems produced by suitable chemical treatment, such as with 1 per cent. nitric acid solution, to form low refractive index surface films; by following this process with a baking operation the glass surface is made much more durable. "Vycor" laboratory ware, which is 96 per cent. silica glass, is practically shockproof thermally; "Pyrex" highway reflecting markers have been pronounced successful by New York State engineers. Several new laboratories for powdered metals research were established. "Plast-Iron," a pure iron powder, was announced. The National Bureau of Standards studied the corrosion of metals used in aircraft. The casting of rods and tubes from molten metal is now performed continuously; wire is made by a process of slitting sheets instead of drawing metal through dies. The reduction of iron ores under pressure by carbon monoxide and the desulfurization of pig iron with calcium carbide were investigated. The output of information on all aspects of welding has continued. Uranium-nickel steels appear to be quite corrosion-resistant; silver-bearing 18/8 stainless steel is much more resistant to chloride solutions than the original alloy. The use of polonium in standard electrode alloys was found to improve the starting performance of spark plugs. Tellurium is employed in a new electric lamp. By an electrolytic process both plating with indium and its production in commercial quantities are possible. It is expected electrorefining of tin will attract more attention in the future. By the middle of 1942 the production of aluminum ingots will have expanded to 250 per cent. of the 1939 level. Advances were made in the knowledge of beryllium-aluminum and beryllium-magnesium alloys. Magnesium production was 13 million pounds in 1940 and will be doubled by the spring of 1942.

New processes were introduced for the stabilization of iodine in iodized carriers. A molten mixture of salts consisting of sodium nitrite and sodium and potassium nitrates is a heating and cooling liquid for industrial processes requiring high temperatures but where direct heating with an open flame is either dangerous or impracticable. The net cost of research in the field of synthetic organic chemicals was about 3½ per cent. of sales. Nitromethane, nitroethane, 1-nitropropane and 2-nitropropane are being manufactured commercially, and later on nitroparaffins with longer carbon chains will be available. Over 80 recently commercialized esters of polyhydric alcohols and their ethers were reported. Normal octanol and normal decanol are now available in quantity; the manufacture of adipic acid was started. The production of guanidine salts was markedly improved. Levulinic acid was made commercially. New nonvolatile, water-soluble compounds, offered under the designation "Carbowax," are recommended for the paper and textile industries and as metal-working

[1] Abstract of a paper prepared for the *News Edition* of the American Chemical Society, published in the issue of January 10.

aids. Sulfathiazole, sulfadiazine and sulfaguanidine are new members of the sulfanilamide family. Drug manufacturers are reported to be studying hydroponics for growing drug plants now produced only in the Orient and for raising the drug content of plants. The four regional laboratories of the U. S. Department of Agriculture were made ready for occupancy. Potassium metaphosphate was described as a potential high-analysis fertilizer material. Better extraction of cottonseed oil is being studied; means are being sought to produce furfural from cottonseed hulls and to use the residual lignin for the production of a plastic. Glues for plywood from cotton and soybean proteins are being developed. Colchicine continued to get attention as an inductor of polyploidy in plants. Applied in the form of a solution containing as little as 1 part in 100 million parts of water, vitamin B_1 is reported to have displayed potentiality in horticulture. "Parmone" is a "liquid hormone spray" containing naphthalene acetic acid, for use in delaying the dropping of fruit from trees until they are ready to harvest. Bactericidal irradiation was put to wider use and the characteristics of the "Sterilamp" were reported. Food dehydration is being studied broadly. There has been considerable activity in research on food antioxidation. A new "synthetic" sausage casing consists of collagen; cholesterol is being produced commercially from beef spinal cords. The growth of research effort in the petroleum industry has been rapid, having expanded 539 per cent. in eleven years and having risen from seventh largest to second largest. The National Advisory Committee for Aeronautics selected Cleveland as the site for the Government's $8,400,000 airplane-engine research laboratory. Geochemical prospecting for underground oil was developed further. The tendency in motor fuels is toward the production of single hydrocarbons or a group of three or four in order that the combustion in automotive engines may be precisely controlled. The new "Polyform" process combining polymerization with cracking was disclosed. At least 10 petroleum refineries are using bauxite for bleaching paraffinic oils. Naphthenic acids extracted from lubricating oil fractions became commercially available. Development of new treatments for lumber is particularly important because much timber now cut is second-growth, which may have a large proportion of sapwood, thus making it more susceptible to staining. Urea is being used as an aid in seasoning lumber; wood can be easily bent by treatment with urea. Lignin has been referred to as the "greatest economic waste in the world to-day," and if ways can be found to hydrogenate lignin cheaply it may become the source of a whole new series of organic compounds. Newsprint was produced from southern yellow pine at Herty, Texas; the U. S. Forest Products Laboratory prepared newsprint by mixing unbleached semi-chemical pulp from southern gum trees with groundwood pulp from southern pine, and at Syracuse University newsprint was made from red pine. "Velo" cold-set ink and nickel ink were described; isophorone is used in improved inks, stencil pastes and roll-coating finishes. Research is in progress on the production of writing paper from low-grade cotton; paper made from cotton burs and stalks is under test in Texas. The U. S. Institute for Textile Research published the results of a broad program of textile-drying investigation; the U. S. Department of Agriculture contributed a new process for sterilizing textile fibers. Uses for cotton discussed by the National Cotton Council, which is supporting extensive investigation at Mellon Institute, included bale coverings, stabilizing road cuts and fills, protecting tree seedlings and beehives, bags for peanuts and fertilizers, and plastics.

"Vinyon" is being utilized in making a variety of felts. The production was announced of "Vinyon" yarn of 74 per cent. greater tensile strength than previously available. Thirty-six mills were licensed to make nylon hosiery and plans were approved for a second plant for the manufacture of nylon yarn at Martinsville, Va., with full operation scheduled for the spring of 1942. Dot patterns are being applied electrostatically on dress goods. The United States now manufactures 96 per cent. of its dyes. Dehydrated castor oil is displaying potentialities in the manufacture of quick-drying paint and varnish; tung oil is being deodorized. Road performance and life studies of low-pressure tires have shown a doubling of mileage since 1927, gains effected through research in materials, design and construction. Electrically conductive rubber is being commercialized. In so-called rubber synthesis researchers are not building a replica of nature's product but are shaping specific molecules to meet particular needs. About 2,000 tons of synthetic rubber were produced in this country during 1939, and around 11,000 tons were made in 1940; plans call for the production of at least 20,000 tons of rubber substitutes by the fall of 1941. A new process deep-draws sheets of cellulose acetate into various shapes. Outdoor furniture is made of woven extruded cellulose acetate-butyrate molding composition. The use of ethyl cellulose, benzyl cellulose, as well as "Vinylite" in commercial floor coverings, has been reported. A training monoplane was built with phenolic-impregnated spruce plywood; the Army Air Corps evolved a Bellanca "plastic plane" whose wings are formed plywood, bonded with a self-setting resin. Tractor seats molded from a soybean protein-formaldehyde plastic are in production. The output of "Vinylite" resins was increased several times and will

be tripled by a new plant. Calendered "Vinylite" sheets have applications as rubber and leather successors, particularly in articles of attire. The development of collapsible tubes formed of vinyl sheet material was reported. "Saran," a vinylidene-chloride thermoplastic resin, is employed in the manufacture of synthetic rattan. The production of melamine resins ("Melamac"), especially for laminating and surface coatings, was announced.

WM. A. HAMOR
MELLON INSTITUTE OF INDUSTRIAL RESEARCH,
UNIVERSITY OF PITTSBURGH

SPECIAL ARTICLES

COMPLEMENT-FIXATION IN ENCEPHALITIS AND RABIES VIRUS INFECTIONS

THE use of brain extracts as an antigen in the complement-fixation test presents considerable difficulties on account of the anti-complementary and non-specific effects involved.[1] Mainly for this reason the test has remained unsatisfactory as a specific method for diagnosing central nervous system virus infections, especially when no other source of antigen than the infected brain is available.

A technique has now been devised, however, by which the disturbing variables have been largely removed or controlled. The main features of the procedure consist in (*a*) preparing the antigens from a heavy brain emulsion by repeated freezing and thawing and centrifugation in the angle head centrifuge; (*b*) inactivating the sera at the proper temperature according to the animal species.

Diluted guinea pig serum constitutes the complement. In each test it is titrated in duplicate in the presence of the antigens, and also in saline. One set of tubes is incubated for one half hour at 37° C., the other at icebox temperature 18 hours before addition of the hemolytic system. The former set at 37° C. determines the amount of complement to use in the later specific test and the latter set at icebox temperature, run with the specific test, indicates the validity of the result by showing the actual amount of free complement present in the system at the time the sensitized blood cells are added. This double titration discloses that some preparations, especially crude brain emulsions, when merely centrifuged in the horizontal centrifuge, show no anti-complementary effect following incubation at 37° C. but do have a strong inhibitory effect when kept in the cold for 18 hours. Thus they are unsuitable as antigens. Antigens prepared as described above, however, usually exhibit no anti-complementary effect until after at least 3 months' aging. The titre of the complement in the presence of antigen is the same as in saline at 37° C. and often even better. Two full units of complement in saline are used in the final specific reaction—an amount equivalent to 2, sometimes 2½ units in the presence of antigen at 37° C. The result of the titration of complement at icebox temperature usually parallels that at 37° C.; besides it gives more exact information on the inhibitory effect of the antigen than the usual antigen control.

TABLE I

EFFECT OF HEATING AT DIFFERENT TEMPERATURES FOR PERIODS OF 20 MINUTES ON THE SPECIFIC AND NON-SPECIFIC COMPLEMENT-FIXING POWER OF SEVERAL NORMAL AND IMMUNE SERA

Sera	56°		60°		65°	
	Homologous antigen	Heterologous antigen or normal brain	Homologous antigen	Heterologous antigen or normal brain	Homologous antigen	Heterologous antigen or normal brain
Rabies immune, Rabbit No. 1	*1/128	1/16	1/128	1/16	1/128	0
" " " No. 2	1/32	1/32	–	–	1/32	0
Eastern equine encephalomyelitis, Rabbit No. 3	1/96	1/24	–	–	1/48	0
Normal, Rabbit No. 4	–	1/16	–	1/16	–	0
Rabies immune, Guinea pig No. 1	1/12	0	1/6	–	1/3	–
" " " " No. 2	1/96	0	–	–	1/24	–
Rabies immune, Mouse (pooled sera)	1/24	1/6	1/12	0	–	–

* 1/128 = Highest dilution at which serum gave a 2+ or better reaction.
0 = No reaction in any of the tubes, the first dilution being usually 1/3 or 1/4.
– = Not tested.

Infected mouse or dog brains have constituted the antigens. A suspension of infected brain is made up in ten times its weight with diluent consisting of 0.85 per cent. saline containing 2 per cent. inactivated normal guinea pig serum. This suspension remains in the icebox 14 to 20 hours and is then spun in a horizontal centrifuge at 2,500 r.p.m. for 30 minutes. The supernatant is removed, frozen and thawed five times in a dry ice-alcohol mixture, and spun in a Swedish angle centrifuge for 1 hour. The supernatant is again removed and, after the addition of 1/10,000 merthiolate, is stored in the icebox.

Sheep red blood cells plus anti-sheep hemolysin constitute the hemolytic system. The hemolysin is

[1] B. F. Howitt, *Jour. Immunol.*, 33: 235, 1937.

titrated at long intervals. 3 M.H.D. of hemolysin and 3 per cent. suspension of packed red cells in saline are employed.

Hyperimmune sera prepared with homologous infected brain tissue have been tested. In contrast to guinea pig sera, rabbit sera usually and mouse sera often give non-specific reactions with unrelated antigens or with normal brain. This effect has been thought to be due to thermolabile substances (Takenomata; Mackie and Finkelstein[2]) and has been removed largely in our tests by establishing temperatures of inactivation for guinea pig serum of 56°, mouse serum, 60°, rabbit serum, 65°. All sera are heated for 20 minutes. This procedure eliminates non-specific as well as anti-complementary reactions without materially disturbing the specific effect (Table I).

The specific reaction is carried out with 0.25 cc of undiluted antigen, plus two full units of complement in 0.5 cc volume, and 0.25 cc of serum. The serum is used in twofold dilutions commencing with 1 to 3 or 1 to 4. These reagents are placed in the icebox 18 hours and then left at room temperature for one half hour. The hemolytic system is then added, consisting of 0.25 cc of the 3 per cent. suspension of sheep cells plus 0.25 cc of hemolysin containing 3 M.H.D. The total volume per tube is then 1.5 cc. The tubes are incubated at 37° C. for one half hour. The degree of hemolysis resulting in each tube is expressed from 0, indicating complete hemolysis, to 4, indicating no hemolysis.

Specific complement-fixation has been obtained with the viruses of St. Louis encephalitis, Japanese B encephalitis, Eastern equine encephalomyelitis, lymphocytic choriomeningitis, louping-ill and rabies (fixed and street). Table II shows the type of result obtained.

Sera have been shown to react in dilutions as high as 1 to 192 and antigens 1 to 128. Rabies antigen is destroyed at 70° C. in 30 minutes. It is affected but little by ultraviolet light irradiation sufficient to render the preparation avirulent. Centrifugation in the high-speed vacuum centrifuge or filtration through Berkefeld N candles, though reducing the virulence considerably (10,000 to 100,000 times), does not alter the antigenicity materially.

TABLE II

COMPLEMENT-FIXATION TESTS WITH MOUSE BRAIN ANTIGENS AND MOUSE IMMUNE SERA

Antigens	Sera inactivated for 20 minutes at 60° C.									
	St. Louis No. 3	Japanese B No. 2604	Japanese B No. 17	Japanese B No. 12	Lymphocytic choriomeningitis	Eastern equine encephalomyelitis	Louping-ill	Rabies (fixed)	Rabies (street)	Saline
St. Louis No. 3	*1/32	0	0	0	0	0	0	0	0	0
Japanese B No. 2604	0	1/32	1/32	1/64	0	0	0	0	0	0
" " No. 17	0	1/32	1/64	1/128	0	0	0	0	0	0
" " No. 12	0	1/32	1/128	1/128	0	0	0	0	0	0
Lymphocytic choriomeningitis	0	0	0	0	1/128	0	0	0	0	0
Eastern equine encephalomyelitis	0	0	0	0	0	1/64	0	0	0	0
Louping-ill	0	0	0	0	0	0	1/64	0	0	0
Rabies (fixed)	0	0	0	0	0	0	0	1/8	1/16	0
" (street)	0	0	0	0	0	0	0	1/8	1/32	0
Saline	0	0	0	0	0	0	0	0	0	–

* 1/32 = Highest dilution at which serum gave a 2+ or better reaction.
0 = No reaction in any of the tubes, the first dilution being usually 1/3 or 1/4.
– = Not tested.

Berkefeld N candles, though reducing the virulence considerably (10,000 to 100,000 times), does not alter the antigenicity materially.

J. CASALS
R. PALACIOS

THE ROCKEFELLER INSTITUTE
FOR MEDICAL RESEARCH,
NEW YORK, N. Y.

ALCOHOLIC AND NON-ALCOHOLIC KETOSTEROIDS AND THE ZIMMERMAN COLOR REACTION[1]

IN the course of isolating steroids from ether extracts of acid-hydrolized urines from cancerous and non-cancerous persons we noticed that the non-alcoholic ketonic fraction of the neutral material contributed considerably to the total 17-ketosteroid titer as determined by the Zimmerman[2] reaction. Since androsterone, a 17-keto hydroxy steroid, is chiefly responsible for the androgenic activity of urinary extracts, this observation may partially explain the divergence existing between the relatively high 17-ketosteroid colorimetric titer and the biological activity.

Evidence has recently been obtained that the non-alcoholic ketonic fraction contains steroid compounds. Burrows *et al.*[3] obtained $\Delta^{3:5}$ androstadiene-17-one

[1] Aided by grants from the Dazian Foundation for Medical Research and the National Research Council Committee for Problems of Sex. Works Progress Administration Project No. 65–1–14–2949.

[2] N. Takenomata, *Zeitschr. Immunitätsforsch,* 41: 508, 1924; T. J. Mackie and M. H. Finkelstein, *Jour. Hyg.,* 28: 172, 1928–29.

[2] W. Zimmerman, *Ztschr. Physiol. Chem.,* 233: 257, 1935.

from the urine of a man with a malignant tumor of the adrenal cortex. Engel[4] isolated two crystalline compounds from the non-alcoholic ketonic fraction of normal male urine. Hirschmann[5] obtained androstenone-17 from the urine of ovariectomized women. We have obtained similar crystallisates from various human urines.[6]

The following table gives the colorimetric titers of (1) the total neutral, (2) the ketonic neutral, (3) the alcoholic ketonic neutral and (4) the non-alcoholic ketonic neutral fractions of a set of pooled urines from non-cancerous and cancerous men and women. The urines were hydrolyzed by boiling for seven minutes after adding concentrated HCl to 15 per cent. by volume. The ketonic material was separated into alcohols and non-alcohols by half-esterification with succinic anhydride.

TABLE 1

THE COLORIMETRIC TITER OF URINARY KETOSTEROIDS IN VARIOUS FRACTIONS OF POOLED HUMAN URINES. ALL VALUES IN MGM EQUIVALENT OF 17-KETOSTEROID PER LITER

Source of urine	Total neutral fraction	Total ketonic fraction	Alcoholic ketonic fraction	Non-alcoholic ketonic fraction
Non-cancerous males .... (188 liters)	14.70	11.62	5.73	5.51
Cancerous males .... (476 liters)	3.90	3.68	1.65	1.73
Non-cancerous females ... (146 liters)	5.69	5.38	2.66	2.00
Cancerous females ... (231 liters)	3.99	3.58	1.74	1.52

It can be seen that roughly half of the titer of the ketones lies in the non-alcoholic fractions. It is interesting that these data on pooled urines confirm previous findings on individual specimens that cancerous persons of both sexes excrete approximately the same amounts of neutral ketosteroids, whereas in the non-cancerous persons there is a clear sex difference and a higher output than in cancerous persons.[7]

If the non-alcoholic ketosteroids are not excreted as conjugated compounds (it is difficult to see how they can be conjugated), then they should be found in full quantity in unhydrolyzed urine. Accordingly, we made a thorough ether extraction of freshly voided male urines (collected from 9 males and extracted within two hours of voiding). This produced 0.3 mgm 17-ketosteroid equivalent per liter of non-alcoholic ketone; the residue after acid hydrolysis yielded an additional 3.2 mgm per liter and 5.1 mgm per liter of alcoholic ketosteroid. We satisfied ourselves by a number of recovery experiments that the separation by succinic anhydride can be successfully carried out on this micro-scale. As little as 50 micrograms of dehydro-androsterone may be isolated in 90 per cent. yield in the alcoholic fraction. The indications, therefore, are that the bulk of the non-alcoholic steroid material arises as a result of the hydrolysis employed.

Since the foregoing findings cast doubt on the probability that the non-alcoholic ketones are true excretion products we have conducted experiments on the effects of acid hydrolysis on androsterone and dehydroandrosterone. Preliminary data indicate that a considerable quantity of each is converted into non-alcoholic material which gives the Zimmermann color reaction. Butenandt and Dannenbaum[8] obtained a chloroketone from urine which they consider a product of HCl hydrolysis. It is notable too that all the non-alcoholic urinary ketones thus far identified might conceivably arise by dehydration of the hydroxyketonic material in the course of acid hydrolysis.

The detailed data of this work and related investigation will be reported elsewhere.

GREGORY PINCUS
WILLIAM H. PEARLMAN
CLARK UNIVERSITY

p-AMINOBENZOIC ACID, A VITAMIN

ABOUT a year ago, Woods and Fildes[1] reported the anti-sulfanilamide activity in vitro of p-aminobenzoic acid. In April, Woods[2] found that yeast extracts contain a substance which nullifies the inhibitory action of sulfanilamide on the growth of hemolytic streptococci, and presented circumstantial evidence that the yeast factor may be p-aminobenzoic acid. In December, Rubbo and Gillespie[3] recovered p-aminobenzoic acid as the benzoyl derivative from yeast and concluded it to be a bacterial growth factor. Experiments conducted in this institute indicate that p-aminobenzoic acid, considered to be an essential metabolite for bacteria by Fildes,[4] is a vitamin, namely, a chromotrichia factor for the rat and a growth-promoting factor for the chick.

One hundred black or piebald rats were placed at weaning age on the basal ration GH–1, consisting of Cerelose 70 per cent., casein 18 per cent., salts 4 per cent., agar 2 per cent., soybean oil 2 per cent., Crisco 2 per cent., and cod liver oil 2 per cent., and received

[3] H. Burrows, J. W. Cook, E. M. F. Roe and F. L. Warren, *Biochem. Jour.*, 31: 950, 1937.
[4] L. L. Engel, *Am. Jour. Physiol.*, 129: P352, 1940.
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[2] D. D. Woods, *Brit. Jour. Exp. Path.*, 21: 74, 1940.
[3] S. D. Rubbo and J. M. Gillespie, *Nature*, 146: 838, 1940.
[4] P. Fildes, *Lancet*, 238: 955, 1940.

daily ½ ml of supplement S–8, a 20 per cent. ethanol solution containing per ml 80 γ each of thiamine hydrochloride, riboflavin and pyridoxine hydrochloride, 1 mg each of calcium pantothenate, nicotinic acid and inositol, and 6 mg of choline chloride. When definite graying of the fur had become apparent, 70 animals received a second daily supplement, namely 1 ml of preparation X–1, a 20 per cent. ethanol solution containing 3 mg/ml of p-aminobenzoic acid (E. K. #14, M. P. 182–4 with decomp.). A bluish discoloration of the skin, a typical first sign of growth of normally pigmented hair, was seen in from two to three weeks and black hair appeared within a month. The 30 control animals, not receiving supplement X–1, continued to show typical achromotrichia.

Chicks reared on the heated vitamin K-deficient ration, recently described,[5] were found to show only a small gain (less than 100 gm) in weight and to die within about a month, even when ample amounts of calcium pantothenate and of the vitamin K-active 2-methyl-1,4-naphthoquinone were fed. However, the addition of 300 γ of p-aminobenzoic acid per gm of ration resulted in better growth and longer survival times. In fact, 78 of 93 birds are still growing at the end of the second month and showed gains in weight of as much as 300 gm in spite of the severe dermatitis symptoms similar to the ones recently described by Hegsted *et al.*[6]

The experiments to date seem to permit the conclusion that p-aminobenzoic acid is one of the factors of the vitamin B complex. Detailed data will appear elsewhere.

S. ANSBACHER
THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH,
DIVISION OF EXPERIMENTAL MEDICINE,
NEW BRUNSWICK, N. J.

SCIENTIFIC APPARATUS AND LABORATORY METHODS

A METHOD FOR MEASURING THE AREA OF SMALL IRREGULAR SURFACES OF THE HUMAN BODY

THE methods[1, 2] previously described for measuring the area of parts of the human body are satisfactory for large or fairly regular surfaces. The area of a small irregular surface such as the pinna of the ear can not be accurately learned by these procedures. The method to be described proved satisfactory for such an area.

Brass plates of known areas, 4 and 10 sq. cm., were covered with a single layer of small lead discs of uniform diameter and thickness (1.02 mm diameter and 0.69 mm thickness) so placed as to reduce bare space to a minimum and held in place with petroleum jelly. The discs were removed, washed free from the jelly and weighed with an accuracy of 0.1 mg. The weight of lead discs necessary to cover one square centimeter could then be calculated. From five separate such measurements 0.601 gm of the discs was found to cover one square centimeter of flat surface. A brass model of known area and similar in shape to the postero-superior portion of the pinna was constructed. The surface of the model was covered with the lead discs and the weight of these discs measured. From the weight of these discs the area of the model was calculated with an error of no more than 2.8 per cent.

A negative cast of the postero-superior portion of the pinna (the part studied is illustrated in Fig. 1) was made of a resilient moulage, Negocoll.[3] Positive casts of dental stone[4] were then made. The positive casts were covered with the lead discs. From the weights of the discs necessary to cover the casts the

FIG. 1. Right pinna. Part of pinna studied is that part above the oblique line.

surface areas were calculated. Duplicate measurements were made in each case. The value of the dupli-

TABLE 1

AREAS OF THE POSTERO-SUPERIOR PORTION OF THE PINNA OF FIVE NORMAL WHITE ADULTS

Subject No.	1	2	3	4	5
Sex	F	M	M	M	M
Age	50	27	30	32	40
Weight of the discs (gm)	13.60	13.28	13.21	13.02	13.86
Area (sq. cm)	8.168	7.981	7.944	7.826	8.319

[5] S. Ansbacher, *Proc. Soc. Exp. Biol. and Med.*, 44: 248, 1940.

[1] E. F. Du Bois, "Basal Metabolism." 3rd ed. Lea and Febiger, Philadelphia, 1936.

[2] H. Isbell, "The Human Finger Tip: Surface Area and Volume Correlations." *Human Biol.*, 11: 536, 1939.

[6] D. M. Hegsted, J. J. Oleson, R. C. Mills, C. A. Elvehjem and E. B. Hart, *Jour. Nutrition*, 20: 599, 1940.

[3] A proprietary preparation of Kern Company, New York City.

[4] Albastone—a preparation of S. S. White Dental Manufacturing Company.

cate measurements agreed within 3 per cent. (Table 1).

The method as described for measuring the area of a portion of the pinna is applicable to other irregular surface areas as well.

GEORGE E. BURCH*
ALFRED E. COHN
CHARLES NEUMANN

HOSPITAL OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK

MELTING POINT APPARATUS

FOR years the senior author has sought for a melting-point apparatus that could be assembled from standard stock glassware and that would yield dependable results with the minimum of effort. We find the following design meets these requirements and possesses certain definite advantages. For example:

(1) A triple-wall air bath is used, minimizing errors due to heat losses and eliminating inflammable or corrosive bath liquids.

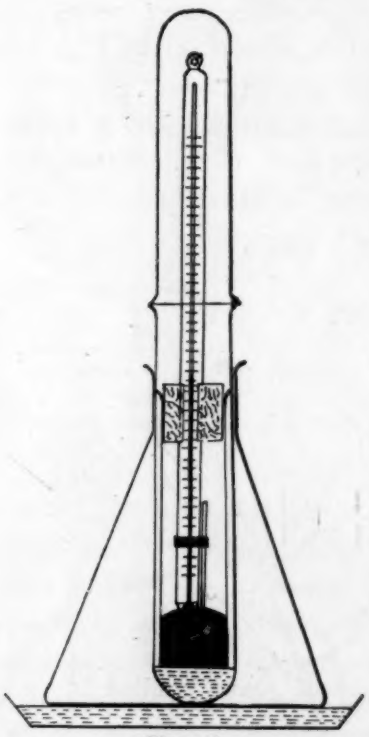

FIG. 1

(2) The thermometer is entirely enclosed, thus obviating uncertain stem corrections.

(3) No stirrer is required.

(4) By surrounding the thermometer bulb with mercury the same temperature is insured for both thermometer and capillary melting tube.

(5) The low cost permits duplication of units to meet the needs of any laboratory.

The apparatus consists of a 250 ml E. flask, pyrex, fitted with a 25 × 200 mm pyrex test-tube, selected so that it will barely pass through the neck of the former, through which it is inserted. A pinch of fine sand is put in the bottom of this test-tube, on which rests a second pyrex test-tube, 18 × 150 mm. The small test-tube contains fifty grams of mercury. In its mouth is a one-hole cork slotted so that the thermometer can be read over the entire scale. A third test-tube 25 mm in diameter is chosen of such length that it will accommodate the thermometer when placed over it to form a closed chamber with the first tube.

A strip of transparent Cellophane tape holds the two test-tubes in alignment. A shallow sand-bath is placed under the flask. The capillary melting tube is adjusted so that the top of its contents extend 1–2 mm above the mercury level, just opposite the thermometer bulb.

The following are typical results, using a stock thermometer:

Benzoic acid, C. P., Eimer and Amend, marked	122
Found	121.7
	121.9
Hydroquinone, Eastman developer, Literature	171.
Found	169.5
Catechol, Merck, resublimed, Literature,	104, 105.
Found	104.2

A. YAUSSY
C. C. KIPLINGER

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* Commonwealth Fund Fellow.